UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,517	02/10/2000	MARCOS DA SILVA FREIRE	3673-2	6833

7590 02/07/2005

NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/423,517	DA SILVA FREIRE ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 January 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on *26 November 2004*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attached*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *71-80 and 82-96*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

ADVISORY ACTION

The amendment filed 1-11-2005 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because: the proposed amendment minimally raise issues under 35 U.S.C. 112, second paragraph. Moreover, the proposed amendment raises new issues that would require further consideration and/or search.

Since Applicant's arguments are predicated on amendments not made of record, said arguments are deemed non-persuasive. Consequently, all pending rejections are maintained for reasons of record and are reiterated below.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 71-80 and 82-96 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a vaccine composition comprising propagating Yellow Fever Virus YF17D in chick embryo fibroblasts, does not reasonably provide enablement for methods producing a human vaccine comprising the propagation of any flavivirus other than YF17D on any cell type other than chick embryo fibroblasts is maintained for reasons of record. The amendment to claims 71 and 80 is

insufficient to overcome the instant rejection. The specification still does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation. Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the applicable factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Applicant argues:

1. The exemplified use of YF17D is sufficient to teach one of ordinary skill in the art to make and use the presently claimed invention.

2. One of ordinary skill in the art will appreciate from the present description those cells that may be used to culture Flavivirus.

3. The references by Post et al. and Theiler et al. exemplify the level of ordinary skill in the art.

Applicant's arguments have been fully considered and deemed non-persuasive.

The instant claims are drawn to methods of producing a human flavivirus vaccine comprising the propagation of a flavivirus in permissive cells wherein said cells are initially seeded at a density of less than $2x10^5$ cells/cm^2 and infected with the seed virus at a multiplicity of infection (MOI) of 0.2-0.0001 infectious units per cell.

With regard to points 1 and 2, the specification provides no guidance as to which flavivirus and cell type other than YF17D and chick embryo fibroblasts could be used in the claimed methods. Moreover, the specification is silent on which flaviviruses are able to infect a given cell type at the claimed MOI. While the specification provides a single working example in which chick embryo fibroblasts are infected with YF17D, it provides no guidelines for extrapolating said working example for use with any other flavivirus or any other cell type. The specification does not provide guidance as to what the cell density should be at the time of infection nor does it provide any guidance as to how the claimed method needs to be adapted for the varying growth rates of differing cell types encompassed by the instant claims. Moreover, as pointed out by Applicant, the prior art would lead one of ordinary skill in the art to use higher cell densities and multiplicities of infection than those used in the claimed methods. While the skill level in arts of cell biology and virology is high, one of ordinary skill in the art would not be able to predict which viruses could be used with a given cell type to produce a productive infection resulting in the production of a human flavivirus vaccine composition utilizing the MOI and cell densities claimed without undue experimentation. Moreover, the specification is silent as to which flavivirus/cell combinations would yield an effective human vaccine. To date, there are not vaccines for all members of flaviviridae hence one of ordinary skill in the art could not contemplate which flavivirus/cell combinations would yield an effective vaccine.

With regard to Point 3, said references are not commensurate in scope with the claimed invention (i.e. are limited to yellow fever viruses) nor do they utilize the same method steps those of the instant invention. Therefore, one cannot extrapolate any conclusions drawn in the cited references to the claimed invention. Moreover, since Applicant failed to point specifically, what portions of the cited references supported his traversal of the instant rejection, any arguments predicated on said references are deemed non-persuasive.

Therefore, given the lack of success in the art, the lack of working examples, and the unpredictability of the generation of a productive flavivirus infection in a given cell type, the specification, as filed, is not enabling for methods producing a human vaccine comprising the propagation of any virus other than YF17D on any cell other than chick embryo fibroblasts.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71-96 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 71 and 85 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (b) of the claimed method is maintained for reasons of record. Contrary to Applicant's assertion to the contrary, one of skill in

the art would not be able to measure and adjust the cell density of culture as recited in the instant claims. The units **cells/cm^2** are used to describe cell densities of adherent cell cultures, whereas cells/ml are the units used for suspension cultures. Consequently it is unclear how the claimed cell density of "less than $2x10^5$ cells/cm^2" applies to cultures. It should be noted that amended dependent claims 75-76 and 89 also recite this language.

The rejection of claims 71 and 85 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (d) of the claimed method is maintained for reasons of record. The amendment to said claims is insufficient to overcome the rejection. The method claims, as amended are confusing. If the cells are in a suspension culture, removing the medium also removes the cells (a separation step is lacking). Moreover, the cell "collection" of step (d) is never refed with culture medium and hence would not be able to survive 144 hours. Moreover, step (f) makes no sense since there is no culture medium to remove from the second incubated cell culture (all culture medium was removed in step (d). Additionally, it should be noted that while step (d) recites the inoculation of the claimed cells with 0.2-0.0001 infectious units per cell, it is unclear what the cell density of the culture is when infected.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

L.F.S.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Robert A. Zeman
February 3, 2005